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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/616,082 | 07/08/2003 | Stephen Hamilton | GFI/107 | 9644 |

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| EXAMINER | |
|---|---|
| JOIKE, MICHELE K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/616,082 | HAMILTON, STEPHEN | |
| | Examiner | Art Unit | |
| | Michele K. Joike, Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

.Applicant's election of Group I in the reply filed on March 10, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Although applicant elected Group I, the claims have been amended to read on Group II. However, pending claims 1-30, which encompass Groups I and II are being examined.

### *Claim Objections*

Claims 2, 10, 12 and 17 are objected to because of the following informalities: An "a" is needed between the word "producing" and "recombinant" in the first line in claim 2. In claims 10 and 12, "is" should be replaced with "has". Claim 17 is a duplicate of claim 15. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for any yeast lacking och1 and other genes encoding mannosyltransferases, does not reasonably provide enablement for any lower

eukaryotic host cell, and specifically not for a yeast cell with no inactivation of a mannosyltransferase, yet comprising a mannosidase capable of hydrolyzing Man$\alpha$1,3 or Man$\alpha$1,6 linkages, or both. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The nature of the invention is a method for producing a recombinant glycoprotein comprising a desired N-glycan in a lower eukaryotic host cell, including a mannosidase capable of hydrolyzing Man$\alpha$1,3 or Man$\alpha$1,6 linkages, or both.

*Guidance of the specification:* Glycoproteins are expressed differently in lower eukaryotes than in higher eukaryotes. Although the first step is highly conserved in all eukaryotes, subsequent processing differs significantly in yeast and requires the addition of several mannose sugars, which are added by mannosyltransferases. The resulting glycan is a "high-mannose" type glycan or a mannan. This differs from the reactions performed in mammalian cells, which involve the removal rather than addition of mannose sugars. It is of particular importance to eliminate the ability of the eukaryotic host cell, e.g., fungus, to hypermannosylate an existing $Man_8GlcNAc_2$ structure. This

can be achieved by either selecting for a host cell that does not hypermannosylate or by genetically engineering such a cell. Hypermannosylation is undesirable for the production of humanoid proteins and it is desirable to reduce or eliminate mannosyltransferase activity. Mutants of *S. cerevisiae* with *och1* or *mnn9* mutations have been shown to be non-lethal. In the examples, only *Pichia pastoris* with an *och1* mutation or *och1* knockout, or a *K. lactis* strain with an *och1 mnn1* double mutant are used.

*Predictability and State of the Art:* Mannan glycans are highly antigenic against mammals. Therefore, it is necessary to eliminate the antigenicity of the sugar chains when recombinant therapeutic proteins are produced in yeast (Chiba et al, J Bio. Chem. 273(41): 26298-26304, 1998, IDS reference). Chiba et al engineered an *S. cerevisiae* strain that inactivated the OCH1, MNN1 and MNN4 genes. Knocking out, or mutating, the OCH1 gene is common when producing mammalian glycoproteins in yeast strains (see, for example, Vervecken et al, Appl. Environ. Microbiol. 70(5): 2639-46, 2004, who inactivated the OCH1 gene in *P. pastoris* for the production of therapeutic proteins.)

The processing of yeast glycoproteins differs from the mammalian glycosylation system. In the second stage of processing N-glycans which occurs in the Golgi, N-glycans are further modified. For yeast, this means adding up to 100 mannose sugars, for mammalians, this means removing mannose sugars. What is required in a yeast system to produce human glycoproteins is to knockout mannosyltransferases, or otherwise block the endogenous core N-glycan biosynthesis and expressing heterologous mannosidases. (Bobrowicz et al, Glycobiology 14(9): 757-766, 2004.)

*Amount of experimentation necessary:* Since the specification only provides examples of yeast strains, and only those with inactivated mannosyltransferases, it is unclear how any lower eurkaryotic host cell could be used in the methods described in claims 1 and 2 and their dependent claims. It would take considerable amount of experimentation to discover how to use a yeast cell, or other lower eukaryotic host cell, without deleting any of the mannosyltransferases to produce therapeutic proteins.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "lower eukaryotic host cell" in claim 1 is used by the claim to mean "A lower eukaryotic host cell, when used herein in connection with glycosylation profiles, refers to any eukaryotic cell which ordinarily produces high mannose containing N-glycans, and thus is meant to include some animal or plant cells and most typical lower eukaryotic cells, including uni- and multicellular fungal and algal cells" (paragraph 115), while the accepted meaning is that lower eukaryotes are restricted to uni- and multicellular fungal and algal cells. The term is indefinite because the specification does not clearly redefine the term. Even within the definition provided, Applicant states

"some animal or plant cells and most typical lower eukaryotic cells, including uni- and multicellular fungal and algal cells", indicating that animal and plant cells are not lower eukaryotes.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 7, 15, 17, 18, 19, 23, 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al.

Applicants teach a method for producing a recombinant glycoprotein comprising a desired N-glycan in a lower eukaryotic host cell, including a mannosidase capable of hydrolyzing at least 10% of the Man$\alpha$1,3 or Man$\alpha$1,6 linkages, or both. The mannosidase is a class II manosidase, which can normally be found in the ER, Golgi apparatus, trans Golgi network or secretory pathway of the cell. The class II mannosidase can be a human mannosidase II. Alternatively, the cell comprises a mannosidase capable of hydrolyzing a Man$\alpha$1,2 linkage. The glycoprotein is isolated from the cell. The cell can be a species of *Saccharomyces*.

Chiba et al (J Bio. Chem. 273(41): 26298-26304, 1998, specifically Figure 1 and Material & Methods) teach a method for producing a recombinant glycoprotein in the ER and Golgi of an engineered *S. cerevisiae*. The *S. cerevisiae* cell lacks functional OCH1, MANN1 and MANN4, to prevent antigenicity of the sugar chains when recombinant

therapeutic proteins are produced. It has an introduced mannosidase capable of hydrolyzing Man$\alpha$1,3 or Man$\alpha$1,6 linkages, or both. The mannosidase is a class II mannosidase, which can normally be found in the ER, Golgi apparatus, trans Golgi network or secretory pathway of the cell. The class II mannosidase is human mannosidase II. The cell also comprises a mannosidase capable of hydrolyzing a Man$\alpha$1,2 linkage. The glycoprotein is isolated from the cell. It is inherent that at least 10% of the Man$\alpha$1,3 or Man$\alpha$1,6 linkages would be hydrolyzed *in vivo,* due to the significant yield of the glycoprotein.

***Allowable Subject Matter***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike, Ph.D. whose telephone number is 571-272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele K Joike, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER